I. Amendments to the Claims

1. (Withdrawn) A filamentous bacteriophage particle displaying on its surface a binding molecule which has a binding domain able to bind target epitope or antigen, wherein the binding domain of the binding molecule consists of a dAb fragment, the particle containing nucleic acid with a nucleotide sequence encoding the binding molecule.

2. (Withdrawn) A filamentous bacteriophage particle according to claim 1 wherein the binding molecule is synthetic.

3. (Withdrawn) A filamentous bacteriophage particle according to claim 2 wherein the nucleotide sequence encoding the binding molecule is provided by combining unrearranged V segments with D and J segments.

4. (Withdrawn) A filamentous bacteriophage particle according to claim 1 wherein the nucleotide sequence encoding the binding molecule is derived by *in vitro* mutagenesis of an existing antibody coding sequence or pre-existing phage antibodies.

5. (Withdrawn) A filamentous bacteriophage particle according to claim 1 wherein the nucleotide sequence encoding the binding molecule is derived from a peripheral blood lymphocyte.

6. (Withdrawn) A filamentous bacteriophage particle according to claim 1 wherein said nucleic acid is comprised in a phagemid genome within the filamentous bacteriophage particle.

7. (Withdrawn) A filamentous bacteriophage particle according to any one of claims 1 to 6, which is in a population of filamentous bacteriophage particles displaying a population of said binding molecules having a range of binding specificities.

8. (Withdrawn) A population of filamentous bacteriophage particles according to claim 7 displaying a population of said binding molecules having a range of binding specificities.

9. (Currently Amended) A method for producing a binding molecule specific for a particular target epitope or antigen, which method comprises the steps of:

producing a population of filamentous bacteriophage particles displaying at their surface a population of binding molecules, wherein each binding molecule in the population of binding molecules has a binding domain and the population of binding molecules has a range of binding specificities, wherein the binding domain of the binding molecules consists of ~~**a dAb fragment**~~ **an antibody heavy chain variable domain**, and wherein each filamentous bacteriophage particle contains nucleic acid with a nucleotide sequence encoding the binding molecule expressed from the nucleic acid and displayed by the particle at its surface;

selecting for a filamentous bacteriophage particle displaying a binding molecule with a desired specificity by contacting the population of filamentous bacteriophage particles with a target epitope or antigen so that individual binding molecules displayed on filamentous bacteriophage particles with the desired specificity bind to said target epitope or antigen.

10. (Original) A method according to claim 9 wherein the binding molecules are synthetic.

11. (Original) A method according to claim 10 wherein nucleotide sequences encoding the binding molecules are provided by combining unrearranged V segments with D and J segments.

12. (Original) A method according to claim 9 wherein the nucleotide sequences encoding the binding molecules are derived by *in vitro* mutagenesis of an existing antibody coding sequence or pre-existing phage antibodies.

13. (Original) A method according to claim 9 wherein the nucleotide sequences encoding the binding molecules are derived from peripheral blood lymphocytes.

14. (Original) A method according to claim 9 wherein said nucleic acid is comprised in a phagemid genome within each filamentous bacteriophage particle.

15. (Original) A method according to any one of claims 9 to 14 additionally comprising separating bound filamentous bacteriophage particles from the target epitope or antigen.

16. (Original) A method according to claim 15 additionally comprising recovering separated filamentous bacteriophage particles displaying a binding molecule with the desired specificity.

17. (Original) A method according to claim 16 additionally comprising

producing in a recombinant system by expression from nucleic acid derived from said separated particles the binding molecule, or a fragment or derivative thereof with binding specificity for the target epitope or antigen, separate from filamentous bacteriophage particles.

II. Preliminary Remarks

A. Interview Summary

The Applicants thank the Examiner for the courtesy and diligence shown during the interview of May 30, 2007, during which the substance of the rejections were discussed.

B. IDS

Regarding the IDS filed on October 20, 2004, which included the Submission of Protective Order Materials Under MPEP § 724; cited references; Petition to Expunge Under 37 C.F.R. § 1.59(b); Supplemental Information Disclosure Statement; PTO Form SB/08A; and stamped-returned postcard, the applicants submit herewith a copy of the listed documents as filed on October 20, 2004.

C. Amendment Support

The claims have been amended to replace the phrase "dAb fragment" with the phrase "an antibody heavy chain variable domain." Support for this amendment is found, for example, on page 3, lines 8-9, which describes molecules which function to bind antigens including "...the dAb fragment (Ward, E. S., et al., *Nature*, 341, 544-546 (1989) which consists of a VH domain..." Example 3 of the specification also describes the insertion of an antilysozyme antibody heavy chain variable domain into a bacteriophage. Figure 1 also depicts an antibody heavy chain variable domain (also referred to in the figure as dAb).

D. Patentability Arguments

The Rejection Under 35 U.S.C. § 102(e) Should Be Withdrawn

The Examiner has maintained the rejection of the claims under 35 U.S.C. § 102(e) as allegedly being anticipated by Dower. The applicants respectfully traverse the rejection and request reconsideration in view of the following.

The pending claims of the instant application as presently amended require that the binding domain of the binding molecule consists of an antibody heavy chain variable domain. The claims of Dower are directed to screening a DNA library for nucleotide sequences which encode "an antibody Fab fragment comprising first and second polypeptide chains, one chain comprising a light chain variable region and another chain comprising a heavy chain variable region." Clearly, as was well known in the art and as described in Dower, Fab molecules are not

the same as antibody heavy chain variable domain. Example 1 of Dower is similarly directed to display of Fab molecules, in which one polypeptide chain composed of VH and CH domains is presented as a fusion with bacteriophage gene III protein and displayed with an associated second polypeptide composed of VL and CL domains to provide a binding domain formed by the VH and VL domains together.

Dower is concerned with provision of multichain proteins in general and Fab molecules in particular, as reflected throughout columns 1-12. Each mention of VH and VL chains throughout Dower is for the identification and cloning, with it being explicitly stated that it is "the binding fragments (Fv) or Fab encoded thereby" that are to be employed, i.e., multichain proteins in which VH and VL domains associate to form a binding domain. *See* for example, Dower, column 3, lines 28-41. The cloning of VH and/or VL domains is further elaborated at Dower, column 4, lines 51-64 where the use of separate cloning vectors for antibody light and heavy chain sequences is suggested from which a combinatorial library is constructed to bring together VH and VL domain sequences in pairs associated to form binding domains. Moreover, in relation to column 4, Applicants direct the Examiner's attention to the fact that this is in relation to use of bacteriophage lambda, which is a lytic phage assembled intracellularly and not a filamentous bacteriophage as required by the instant claims. Furthermore, the reference is explicitly to expression, not display and citation is given to Huse *et al.*, Science 246:1275-1281 (1989) and Short *et al.*, Nucleic Acids Res. 16:7583 (1988), both of which are concerned with expression from lambda vectors and not bacteriophage display. Thus, Dower relates to display of multichain proteins, mostly Fab, with a suggestion of Fv, and not antibody heavy chain variable domains as required by the present claims. Accordingly, Applicants respectfully submit that claims 9 and 15-17 are not properly anticipated by Dower and hereby request withdrawal of the rejections under U.S.C. §102(e).

1. The Rejection of Claim 9 Under 35 U.S.C. §103 Should be Withdrawn

The Examiner has also maintained the rejections under 35 U.S.C. §103(a) as allegedly unpatentable over WO 90/02809 (hereinafter "Ladner and Guterman") and WO 88/06630 (hereinafter "Ladner *et al.*"). The Examiner characterizes Ladner and Guterman as teaching display of binding domains, encoded by nucleic acid sequences, on the surface of filamentous bacteriophage and screening via binding to targets. The Examiner further characterizes Ladner

and Guterman as failing to expressly convey the expression of antibody fragments on the surface of filamentous phage. The Examiner characterizes Ladner *et al.* as teaching methods of displaying SCADs or single-chain antibodies on the surface of Lambda phage and screening against antigens. The Examiner alleges variously throughout the file history that it would have been obvious to one of ordinary skill in the art at the time the invention was made "to alter the methods of screening filamentous phage displaying proteins of Ladner and Guterman with the SCADs or antibody fragments of Ladner et al."

The Examiner's rejection of claim 9 under 35 U.S.C. §103(a) relies on the Examiner's belief that Ladner *et al.* discloses use of molecules that are an essential component of the present claims, i.e. that Ladner *et al.*'s "SCADs" equate to VH domains of antibodies. In fact, the "SCADs" of Ladner *et al.* are more commonly known as scFv or single-chain Fv molecules which consist of a VH domain and a VL domain joined by a peptide linker so that the binding domain is composed of the VH and VL domain. As presently amended, the claims recite *"an antibody heavy chain variable domain"* as the only binding domain present on the surface of phage. In other words, the present invention is concerned with <u>different molecules</u> from those of Ladner *et al.* Further, Lambda phage disclosed in Ladner is not a filamentous phage as is required by the present claim.

The nature of the SCAD's can be understood from the material presented in Ladner *et al.* as the source of the term, i.e., copending U.S. Patent Application No. 10/902,970. U.S. Patent Application 10/902,970 issued as U.S. patent 4,704,692 (hereinafter the "'692 patent"). The '692 patent teaches a method for "generating single chain structures from two-chain aggregate structures, wherein the single chain will retain the three-dimensional folding of the separate natural aggregate of two polypeptides chains." See '692 patent, column 2, lines 31-35. One of ordinary skill in the art would understand that the '692 patent teaches the creation, in a single polypeptide chain, of a replica of an Fv molecule, which is a two-chain molecule consisting of a VH domain and a VL domain associating to form a single binding domain. *See* also, e.g., '692 patent, figures 6B and 7.

Accordingly, the combination of Ladner and Guterman with Ladner *et al.* does not teach or suggest the display of an antibody heavy chain variable domain on the surface of a filamentous bacteriophage, and therefore cannot properly render claim 9 obvious. In view